Heteroresistance of *Mycobacterium tuberculosis* Strains May Be Associated More Strongly With Poor Treatment Outcomes Than Within-Host Heterogeneity of *M. tuberculosis* Infection

To the Editor—We read with great interest Cohen et al's analysis of within-host heterogeneity of *Mycobacterium tuberculosis* infection and its association with poor early treatment response [1]. Their main conclusion that "the presence of a complex infection was independently associated with a nearly 2-fold increased odds of persistent culture positivity" [1p1798] was based only on results of mycobacterial interspersed repetitive units–variable number of tandem repeats analysis. However, as listed in Table 2 of their article, the multidrug-resistant (MDR) disease at baseline seemed to be associated more strongly with a nearly 4-fold increased odds of persistent culture positivity (adjusted odds ratio [aOR], 3.84) than the presence of a complex infection (adjusted odds ratio [aOR], 1.90). The authors should explain why they selected molecular typing results over the heteroresistance of the MDR disease for their analysis. In addition, the authors mentioned in the Discussion section that, "because our follow-up ended at 2 months, we were unable to examine the relationship between complex infections and final treatment outcome" [1p1798]. As readers, we would like to know why the follow-up had to end at 2 months, especially when only 77 patients would need to be followed, and results about the relationship between complex infections and final treatment outcome would have made this article more meaningful.

We agree with the authors that the clinical management of tuberculosis, especially MDR tuberculosis, is a major challenge in resource-limited regions, such as South Africa and rural areas of China. The fifth national tuberculosis survey in China showed that high percentages of tuberculosis cases were drug resistant and the 6.8% were MDR [2]. The prevalence of MDR tuberculosis in Zunyi, Guizhou Province, China, was even higher [3], which indicated the necessity to determine drug susceptibility patterns for improving treatment outcomes of patients with drug-resistant tuberculosis.

Three groups of antituberculosis drugs are recommended by the World Health Organization as the standardized regimens for treatment of patients with MDR tuberculosis if susceptibility is documented or suspected. However, only 50% of patients with MDR tuberculosis and 26% of patients with extensively drug-resistant (XDR) tuberculosis who started treatment in 2012 had successful outcomes of treatment [4]. Previous studies showed that individualized treatment regimens seemed to have a higher treatment success rate (64%) than standardized regimens (54%) for MDR tuberculosis [5], and factors associated with worse outcome included smear positivity at diagnosis, fluoroquinolone resistance, and the presence of an XDR resistance pattern [6]. Within-host heterogeneity of *M. tuberculosis* infection could be one of the factors affecting treatment outcomes [1]. A recent study also showed that high rates of treatment success (72.2%) could be

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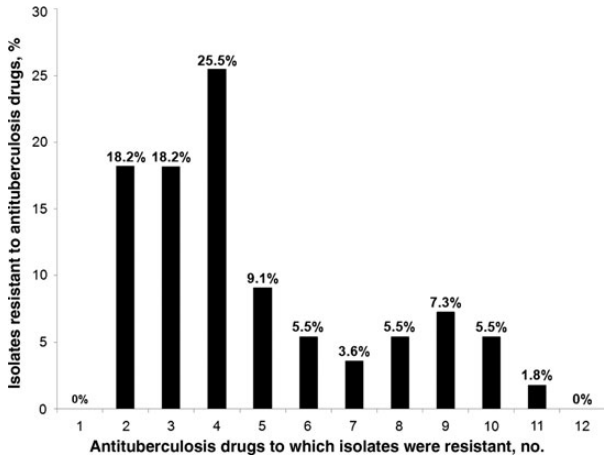

Figure 1. Drug resistance patterns of 55 multidrug-resistant *Mycobacterium tuberculosis* isolates from Zunyi, Guizhou Province, China. Fifty-five multidrug-resistant *M. tuberculosis* isolates were tested for susceptibility to 4 first-line antituberculosis drugs (isoniazid, rifampicin, ethambutol, and streptomycin) and 8 second-line antituberculosis drugs (levofloxacin, gatifloxacin, moxifloxacin, amikacin, kanamycin, capreomycin, prothionamide, and para-aminosalicylic acid), as described previously [8]. The hetero-resistance of multidrug-resistant *M. tuberculosis* isolates is displayed as a percentage of isolates resistant to various numbers of antituberculosis drugs.

achieved in patients with MDR/XDR tuberculosis by individually tailored treatment regimens [7].

To minimize adverse reactions and improve treatment outcomes for patients with MDR tuberculosis, we determined drug susceptibility patterns of 55 clinical MDR *M. tuberculosis* isolates from Zunyi for 12 antituberculosis drugs. Our results indicated that there were 24 different drug resistance patterns among 55 MDR *M. tuberculosis* isolates; only 10 (18.2%) were resistant to rifampicin and isoniazid, 35 (63.6%) were resistant to ≥4 drugs, and 1 (1.8%) was resistant to 11 drugs (Figure 1). Our results demonstrate that clinical isolates from patients with MDR tuberculosis could have many different drug resistance patterns (Figure 1), which explains partially why standardized regimens seemed to have lower treatment success than individualized treatment regimens. Our unpublished studies showed that higher rates of treatment success (about 70%) could be achieved in patients with MDR tuberculosis by individually tailored treatment regimens based on their drug resistance patterns, rather than the standardized regimens (about 50%).

Based on our studies and data listed in Table 2 of the article by Cohen et al [1], we predict that heteroresistance of *M. tuberculosis* strains may be associated more strongly with poor treatment outcomes than within-host heterogeneity of *M. tuberculosis* infection. Cohen et al would be able to approve or disapprove this prediction if they could determine drug resistance patterns of 77 *M. tuberculosis* strains collected at the end of their 2-month study [1].

Notes

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